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Brief Clinical Report

Prenatal Ultrasonographic Findings of Dominant Polycystic Kidney Disease and Postnatal Renal Evolution

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Autosomal dominant polycystic kidney disease (ADPKD) is a relatively common genetic disorder, and its prenatal diagnosis has been reported with increasing frequency. Nevertheless, no data are available on the significance of prenatal ultrasound (US) patterns in predicting postnatal renal function and outcome. We report on one case of ADPKD diagnosed prenatally by US, and on two cases diagnosed immediately after birth, with different prenatal US and renal outcomes. Data on prenatal US findings and postnatal renal evolution are scanty and largely incomplete. Apparently, none of the prenatal findings are consistently different in cases with and without normal postnatal renal function and blood pressure. More complete information on prenatal US findings and postnatal renal evolution is urgently needed. © 1996 Wiley-Liss, Inc.

KEY WORDS: prenatal diagnosis, autosomal-dominant polycystic kidney disease, ultrasonography

INTRODUCTION

With the widespread use of ultrasound in pregnant women and genetic studies, the number of prenatal diagnoses of autosomal-dominant polycystic kidney disease (ADPKD) has increased [Ceccherini et al., 1989; Fick et al., 1993; Gagnadoux and Habib, 1989; Garel et al., 1982; Journel et al., 1989; Main et al., 1983; McHugo et al., 1988; Novelli et al., 1989; Pretorius et al., 1987; Sedman et al., 1987; Turco et al., 1992; Zerres et al., 1982]. Nevertheless, no data are available on the significance of prenatal echographic patterns in predicting postnatal renal function and evolution. We report on 3 infants with ADPKD investigated prenatally by ultrasound (US), with different renal outcomes. Based on personal experience and previous reports, we discuss the possibility of predicting renal outcome from prenatal US patterns.

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MATERIALS AND METHODS

Hypertension was defined as having diastolic or systolic blood pressure >95th centile for age [Task Force on Blood Pressure Control in Children, 1987]. Renal function was determined by serum creatinine and by creatinine clearance corrected for 1.73 m^2 body surface area. US evaluation was performed using high-definition and high-frequency probes (5–7 MHz) which are able to identify small cysts with a diameter of 1.5–2 mm. We selected cases from the literature based on the following criteria: presence of prenatal and postnatal ultrasonographies, reported renal function, blood pressure, and follow-up.

Case 1

Family history was unremarkable. Oligohydramnios [Phelan et al., 1985] was first demonstrated at gestational age 4 months. Kidneys were reported as "normal." An asphyctic female infant was born at term with a birth weight of 3400 g. The first 2 months of life were characterized by failure to thrive. Her clinical condition worsened and, during the second month, she was admitted in coma. She had renal failure and hypertension (plasma creatinine 560 μmol/l, B.P. 160/90 mmHg). Abdominal US showed bilateral renal enlargement (95th centile), loss of cortico-medullary differentiation with increased echogenicity, and numerous cortical cysts up to 8 mm in size. The liver was normal. A diagnosis of ADPKD was suggested. Renal US findings were normal in the mother but showed many previously unknown renal cysts in the 32-year-old father, who was also discovered to have mild chronic renal failure (CRF). Plasma creatinine was 133 μmol/l, creatinine clearance

was 66 ml/min. The paternal grandfather, 64 years old, was also found to have renal cysts and arterial hypertension. At age 5 months the patient was started on peritoneal dialysis, and at age 3 years she received a cadaveric transplant. Nephrectomy performed on this occasion confirmed the diagnosis of ADPKD. DNA analysis was carried out on all available relatives. The following polymorphic markers, flanking the ADPKD-1 locus on 16p13, were examined using Southern blotting: 3′HVR/*Pvu*II, 3′HV/*Bg*III, 3′HVR/*Bg*II, EK-MDA/*Tag*I, PGGl/*Pst*I, CMM65/*Tag*I, 24–1/*Tag*I. The at-risk haplotype, D-O-d-te-U4-M2-B2, was found in the proposita, her father, one paternal uncle, and paternal grandfather.

Case 2

A second pregnancy occurred in the same family when the proposita (case 1) was 2 years old. DNA analysis was carried out on a chorionic villous biopsy sampled at 10 weeks of gestation. The chromosomally normal female fetus had inherited the haplotype at risk. Thus, we predicted a 99% probability for this fetus to be affected. At 16 gestational weeks kidney structure and amniotic fluid volume were considered normal. At 24 gestational weeks reduction of amniotic fluid [Phelan et al., 1985] was found with increased kidney volume (4.3 cm and 4.1 cm) and echogenicity (Fig. 1). No cysts were seen. These findings were confirmed by subsequent US study at 26, 28, and 33 weeks of gestation. Weight at birth was 3,000 g. Plasma creatinine was 47 μmol/l, and BP was normal. Renal US study performed in the first day of life showed large, echogenic kidneys and numerous cysts, findings that were confirmed 3 weeks later (Fig. 2). Liver was normal. Intravenous pyelography (IVP) also showed irregular renal outlines and stretched calices. US study at age 2 months showed enlarged kidneys (5.1 and 5.2 cm) with more than 20 cysts in both kidneys. Maximum cyst diameter was 4–5 mm, with most having a diameter of 2 mm. Maximum size of the cysts during the first year of life was between 4–8 mm. Renal function remained reduced but did not deteriorate throughout the third year of life. Creatinine clearance was 25 ml/min/1.73 m^2 during the first 3 months of life, and 51 ml/min/1.73 m^2 at age 4 years. BP remained normal. Statural growth remained at <3rd centile.

Case 3

Obstetrical US was performed at weeks 21 and 33 of gestation because the father and paternal grandmother were affected by ADPKD. Amniotic fluid and kidneys were normal. A female baby was born at 40 weeks with a birth weight of 3,200 g and normal renal function (plasma creatinine 40 μmol/l, creatinine clearance 77 ml/min/1.73 m^2). The first renal US study at age 3 months showed enlarged kidneys (7 cm) with increased parenchymal echogenicity, and loss of cortico-medullary differentiation. No cysts were detected. Renal US study at age 18 months showed enlarged kidneys (8.2 cm), increased echogenicity, and the presence of small cysts with a maximum size of 2 mm. At last observation at age 18 months, plasma creatinine was 44 μmol/l, creatinine clearance was 80 ml/min/1.73 m^2, maximum urine osmolality was slightly abnormal (766 mosm/KgH_2O), and BP was normal.

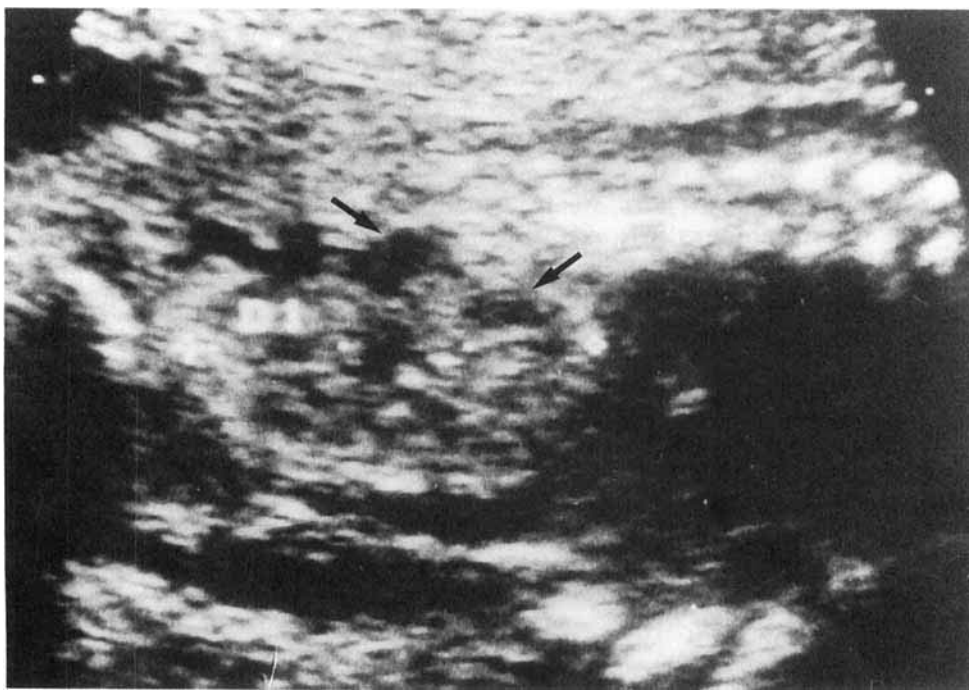

Fig. 1. Echography at 33 weeks of gestation (3.5 MHz), showing enlarged kidney with increased cortical echogenicity. Cortical-medullary differentiation is present, and pyramids (arrows) are clearly visible. No cysts are detected.

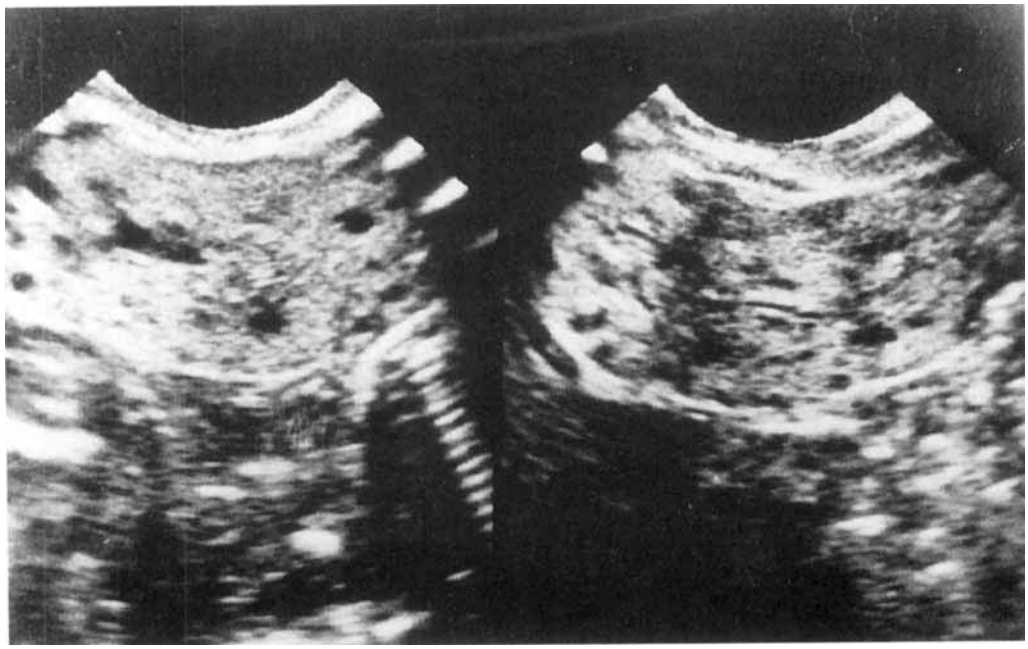

Fig. 2. Renal echography at age 3 weeks. High-frequency (7.5 MHz) probe analysis reveals numerous small cysts and loss of cortico-medullar differentiation. Both kidneys are enlarged.

DISCUSSION

The widespread use of prenatal US and DNA analysis has led to an increased number of prenatal ADPKD diagnoses. Pediatricians, pediatric nephrologists, and obstetricians are (and will be even more in the future) urged to provide information on possible renal outcome in those cases diagnosed early during pregnancies. However, at present, postnatal renal evolution in children prenatally diagnosed with ADPKD is not sufficiently well-documented despite the number of published cases [Ceccherini et al., 1989; Fick et al., 1993; Gagnadoux and Habib, 1989; Garel et al., 1982; Journel et al., 1989; Main et al., 1983; McHugo et al., 1988; Novelli et al., 1989; Pretorius et al., 1987; Sedman et al., 1987; Turco et al., 1992; Zerres et al., 1982]. We collected prenatal and postnatal US findings and renal function parameters from known prenatally diagnosed patients with ADPKD, including the 3 cases in this report (Table I). A total of 23 cases was available, 6 of whom had impaired postnatal renal function at an age ranging from birth to 36 months. It is evident how often the information given is very incomplete. Seventeen cases had normal renal function at an age ranging from 2 days–84 months. In the first group, oligohydramnios was present in 2 of the 3 cases on whom this information was available. Normal amniotic fluid volume was reported in one case only, at 31 weeks of gestation. Another fetus with oligohydramnios was reported [Novelli et al., 1989] but was aborted at 27 weeks.

In the second group, only 1 of 9 cases with this information was reported to have had "slightly reduced amniotic fluid" at 23 weeks of gestation [McHugo et al., 1988]. The presence of oligohydramnios, prenatally enlarged kidneys, increased echogenicity, and presence of cysts did not appear significantly more common in the two groups (by χ^2 test). This also applies to US findings evaluated immediately after birth. Our cases also prove that the absence of renal cysts in late pregnancy by US does *not* exclude their presence at birth. Problems in using high-frequency probes for studying fetal kidneys during pregnancy probably explain the difficulty in identifying renal cysts, even in those cases where they become evident neonatally, when high-frequency probes can be used. At present, reduced amniotic fluid could be considered a possible prenatal prognostic indicator in ADPKD patients, but the data reported are too scanty and incomplete. Close scrutiny of US findings in fetuses at risk for ADPKD, and systematic investigation of renal function at birth and during the first year(s) of life, will improve current understanding of prognostic parameters in these fetuses and children.

ADPKD is a heterogeneous disease. A large collaborative study demonstrated that, in about 14% of families, the gene defect is not located on chromosome 16 [Peters et al., 1993]. Recent results have shown that a second locus for ADPKD (PKD2) is located on 4q [Peters et al., 1993]. Different from ADPKD families linked to chromosome 16 (PKD1), PKD2 patients are diagnosed at an older age, have fewer cysts, are less likely to have hypertension, with a slower progression towards renal failure. Thus, it is likely that all ultrasonographically-diagnosed fetuses have PKD1. Numerous cases affected by ADPKD with fetal and neonatal presentation appear to cluster in families [Zerres et al., 1993]. Ages at onset show a striking similarity in affected sibs, regardless of age of initial presentation in

TABLE I. ADPKD Cases From the Literature With Prenatal and Postnatal US and Renal Function Parameters, Including Our 3 Cases*

Source	Case	Prenatal					Postnatal							Outcome			
										No. of cysts		Maximum size (mm)					
		G.A.	A.F.	Size	Echog.	Cysts	Size	Echog.	Cysts	r.	l.	r.	l.	Age (months)	P. cr. (μmol/l)	B.P. (mm Hg)	Renal function
Garel et al. [1982]	1	28	NR	NR	NR	+	+	+	+	NR		20–>40		birth	NR	+	RDC
Pretorius et al. [1987]	1	31	N	N	N	NR	N	NR	+	2		NR		25	300	NR	RDC
Gagnadoux and Habib [1989]	1	36	NR	+	+	–	NR	NR	NR	NR		NR		36	NR	NR	RDC
Fick et al. [1993]	1	28	NR	+	N	–	N	N	+	1	5	NR		11	50	+	RDC
Present case	1	28	RDC	?	?	?	+>95°	+	+	>25	>20	11	7	36	81	+	RDC
	2	24	RDC	+	+	–	75°	+	+	>20	>30	9	8	48	92	N	RDC
	3	33	N	N	N	–	+>95°	+	+	NR		2	2	18	50	N	N
Zerres et al. [1982]	1	33	NR	+	NR	+	++	NR	+	NR		NR		12	NR	NR	N
Main et al. [1983]	1	36	N	N	NR	+	+>95°	NR	+	NR		NR		2	NR	N	N
	2a	30	N	+	+	NR	+>95°	NR	NR	NR		NR		6	NR	N	N
	2b	30	N	N	N	–	+<95°	NR	NR	NR		NR		6	NR	N	N
McHugo et al. [1988]	1a	32	N	+	+	–	+	+	+	2	0	5	0	8	NR	N	N
	1b	32	N	N	N	NR	N	N	–	–	–	–	–	8	NR	N	N
	2	23	RDC	+	+	–	+	+	–	–	–	–	–	2 days	NR	N	N
Journel et al. [1989]	1	35	NR	+	+	NR	+	+	+	4	5	10	11	NR	NR	NR	N
	2	35	NR	+	+	NR	NR	NR	NR	–	–	–	–	7	NR	NR	N
Pretorius et al. [1987]	1	36	N	+	++	+	+	+	+	1		30		NR	NR	+	N
	2	31	N	+	+	–	+	+	+	NR		2–>3		8	NR	N	N
Gagnadoux and Habib [1989]	1	34	NR	+	+	–	NR	NR	NR	NR		NR		36	NR	NR	N
Fick et al. [1993]	1	36	NR	+	++	+	+	+	+	>15	>15	NR		24	NR	+	N
	2	21	NR	+	+	–	+	+	+	5	>15	NR		8	NR	+	N
	3	In utero	NR	+	+	–	+	+	+	6	4	NR		84	NR	+	N
Turco et al. [1992]	1	20	NR	+	NR	+	+	+	+	NR		25		5	NR	N	N

* G.A., gestational age; A.F., amniotic fluid; N.R., not reported; N, normal; RDC, reduced; Echog., echogenicity; P. cr., plasma creatinine; B.P., blood pressure.

their parents, which would be in adult life. A bimodal onset distribution of the disease in childhood was observed [Taiz et al., 1987]. A polycystic breakpoint (PRP) gene has been cloned from the PKD1 region [European Polycystic Kidney Consortium, 1994]. Mutations of the PRP gene have been found only in a small number of patients, which confirms that PRP is in the $ADPKD_1$ gene [Turco et al., 1995]. This PKD1 product is an extracellular matrix protein present in kidney, liver, and cerebral blood vessels. However, despite progress in understanding the PKD1 genetic defect, the causes of the great variability in clinical expression of the disease are unknown. Further studies based on prospectively collected US and renal function data are urgently needed.

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